Complete Summary

GUIDELINE TITLE

Adjuvant chemotherapy following complete resection of soft tissue sarcoma in adults.

BIBLIOGRAPHIC SOURCE(S)

Figueredo A, Bramwell VHC, Bell R, Davis AM, Charette ML, Sarcoma Disease Site Group. Adjuvant chemotherapy following complete resection of soft tissue sarcoma in adults [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Oct. 27 p. (Practice guideline; no. 11-2). [43 references]

Figueredo A, Sarcoma Disease Site Group, Bramwell VH, Bell R, Davis AM, Charette ML. Adjuvant chemotherapy following complete resection of soft tissue sarcoma in adults: a clinical practice guideline. Sarcoma 2002;6:5-18. [41 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Soft tissue sarcoma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To make recommendations on the benefits of anthracycline-based adjuvant chemotherapy in adult patients with completely resected soft tissue sarcomas, in terms of local disease control, systemic recurrence and overall survival
- To make recommendations on what circumstances should adjuvant chemotherapy be recommended in the context of benefits and expected toxicities
- To make recommendations on any advantages in using combination versus single-agent anthracycline-based chemotherapy in the adjuvant setting

TARGET POPULATION

Adult patients with resected soft tissue sarcoma

INTERVENTIONS AND PRACTICES CONSIDERED

1. Single-agent doxorubicin
2. Combination chemotherapy with vincristine + doxorubicin + cyclophosphamide + actinomycin D (VACAR)
3. Combination chemotherapy with vincristine + cyclophosphamide + actinomycin D/ vincristine + doxorubicin + dacarbazine (VAC/VAD)
4. Combination chemotherapy with doxorubicin + cyclophosphamide/methotrexate + leucovorin (AC/MTX)
5. Combination chemotherapy with cyclophosphamide + vincristine + doxorubicin + dacarbazine (CYVADIC)

MAJOR OUTCOMES CONSIDERED

- Disease relapse
- Disease-free survival
- Overall survival
- Toxicity from treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

Original guideline: November 2000

The recently published exhaustive reviews of the literature and clinical trial registries form the basis for the present overview. MEDLINE (Ovid) (1996-August 2000), CANCERLIT (Ovid) (1996-June 2000) and the Cochrane Library (Issue 3, 2000) were searched for additional trials published since the latest overview using the terms: "sarcoma" (Medical Subject Heading [MeSH]), "soft tissue sarcomas" (text words), "postoperative" (text word), "adjuvant therapy" (text word) and adjuvant chemotherapy (MeSH and text word). These terms were then combined with the search terms for the following study designs: practice guidelines, systematic reviews or meta-analyses, reviews, randomized controlled trials and controlled clinical trials. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/), and the proceedings of the 1997-2000 annual meeting of the American Society of Clinical Oncology (ASCO) were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed by one member of the Sarcoma Disease Site Group and methodologists, and the reference lists from these sources were searched for additional trials.

Update: October 2002

The original literature search has been updated using MEDLINE (through September 2002), CANCERLIT (through August 2002), the Cochrane Library (Issue 3, 2002) and the 2001-2002 proceedings of the annual meeting of the American Society of Clinical Oncology. The PDQ database on the Internet was also searched for reports of any new trials and updates to the status of ongoing trials.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. Randomized controlled trials (RCTs) comparing anthracycline-based adjuvant chemotherapy to observation in patients with completely resected soft tissue sarcoma
2. Patients were at least 15 years of age
3. Data provided on outcomes of overall and disease-free survival
4. Abstracts of trials were considered

Exclusion Criteria

1. Phase I and II studies were not considered for inclusion in this report because of the availability of randomized controlled trials
2. Letters and editorials were not considered
3. Papers published in a language other than English were not considered.

NUMBER OF SOURCE DOCUMENTS

Four meta-analyses and 17 randomized controlled trials met the inclusion criteria and were reviewed.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Summarized Patient Data
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Original: November 2000

A published figure from the Sarcoma Meta-Analysis Collaboration (SMAC) has been used to provide data on disease relapse and survival (see figure 1 in original guideline document). To investigate outcome results versus type of therapy (single-agent versus combination chemotherapy), the data were reanalyzed by the Sarcoma Disease Site Group using the software package Metaanalyst[0.098] (provided by J. Lau, Boston, MA, USA). To estimate overall effects, and to maintain uniformity with previous meta-analyses, the odds ratio (95% confidence intervals) is reported according to the fixed effects model of Mantel-Haenzel and Peto. Estimates for odds ratios (OR) >1.0 favour the control group (observation) whereas OR <1.0 favour the treatment group (adjuvant chemotherapy). In addition, the individual published trials have been analyzed for chemotherapy toxicity and compliance.

Update: October 2002

Because the SMAC meta-analysis was performed using individual patient data, and this level of data is not available for the new trials identified through updating activities, a new meta-analysis incorporating these trials has not been done as of October 2002. Overall, the results of these new trials are consistent with the results of the trials examined by the SMAC.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

November 2000 Guideline

The benefits in preventing disease relapse and improving patient survival, especially in patients with resected soft tissue sarcoma (STS) of the extremities, although modest, compare favourably with results for adjuvant chemotherapy in early breast cancer and stage III colon cancer, where adjuvant therapy is considered standard care. The Sarcoma Meta-Analysis Collaboration (SMAC) database used to draw these conclusions is, however, much smaller than similar databases for the other common tumours. With this limitation, doxorubicin-based adjuvant chemotherapy can be reasonably considered for adult patients with resected STS of the extremities at high risk of recurrence (deep high grade tumours >5 cm in size) and at low risk of adverse effects (no underlying diseases, particularly cardiovascular).

The information related to the effect of chemotherapy on local control should be interpreted with some caution. In the SMAC meta-analysis, 15% of patients treated with chemotherapy experienced local recurrence (101 of 659 cases), compared with 19% (126 of 656 cases) in the control group. These relatively high rates of local recurrence are of concern. Local treatment is most important in the initial management of sarcomas. In extremity sarcomas, wide surgical excision, supplemented by radiation in cases where tumour size or location limits the procedure, can achieve local control in over 90% of cases. However, the meta-analysis did not separately assess the local recurrence rate for extremity sarcomas. The higher rate of local recurrence reported may be explained by the inclusion of non-extremity sarcomas, which are known to have a higher rate of local failure.

The consideration of doxorubicin-based adjuvant chemotherapy for patients with STS at non-extremity locations is more problematic. There are limited data about these tumours, and the available trials are inconclusive as to benefits with respect to disease relapse or survival. Due to the fact that there are few trials investigating patients with retroperitoneal sarcomas, and the observed adverse effect of chemotherapy on survival (when combined with radiation therapy [RT]), doxorubicin-based adjuvant chemotherapy cannot be recommended for retroperitoneal sarcomas. The data on uterine sarcomas are based mostly in a single trial with negative results; therefore, no specific recommendation can be made about these tumours. Gastrointestinal stromal tumours (GIST) should now be considered separately from other STS; most GIST constitutively express a cKIT receptor and are responsive to imatinib mesylate. The role of this drug as adjuvant therapy is currently being evaluated in clinical trials. The Sarcoma Disease Site Group (DSG) is in the process of developing an evidence summary on the use of imatinib mesylate as palliative treatment for patients with unresectable or metastatic GIST expressing cKIT.

The search should continue for more effective adjuvant therapies. It was not possible to demonstrate a larger benefit for doxorubicin-based combination chemotherapy compared with single-agent doxorubicin. This may be due to the fact that some of the combination regimens in the SMAC database are not considered useful today. On the other hand, combination chemotherapy with ifosfamide (the second most active drug in advanced STS) is only represented by a small study with 31 patients. The significant results of the second Rizzoli trial using intensive epirubicin and ifosfamide supported by granulocyte-colony stimulating factor (G-CSF) should be pursued in future clinical trials. Strategies for reducing anthracycline-induced cardiotoxicity should be investigated. This

approach may have limitations, as the use of doxorubicin by infusion compared with the drug given by bolus reduced not only cardiotoxicity but also disease-free and overall survival. Because of problems with toxicity and drug compliance, patient quality of life should be investigated and reported. As the meta-analyses have shown, a large number of patients will be required to demonstrate significant differences in outcomes, and these trials will require international cooperation.

October 2002 Update

The conclusions described above remain current.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This practice guideline report has been reviewed and approved by the Sarcoma Cancer Disease Site Group, which comprises medical oncologists, radiation oncologists, surgeons, a pathologist, a methodologist and community representatives.

External review by Ontario practitioners was obtained through a mailed survey of 78 practitioners (26 medical oncologists, 14 radiation oncologists, 32 surgeons, two pathologists, and four gynecologists) consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Written comments were invited. Follow-up reminders were sent at two-weeks (post card) and four weeks (complete package mailed again). Forty-six (61%) surveys were returned.

Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The practice guideline report was originally completed on November 10, 2000 and published in Sarcoma, Volume 6, Number 1, 2002. The guideline was reviewed in October 2002.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- It is reasonable to consider anthracycline-based adjuvant chemotherapy in patients who have had removal of a sarcoma with features predicting a high likelihood of relapse (deep location, size >5 cm, high histological grade). These features correspond to International Union Against Cancer (UICC) stage III.
- Although the benefits of adjuvant chemotherapy are most apparent in patients with extremity sarcomas (7% risk difference for overall survival at 10 years), patients with high-risk tumours at other sites should also be considered for such therapy.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Four meta-analyses and 17 randomized controlled trials (RCTs) met the inclusion criteria and were reviewed. Fourteen of the randomized controlled trials were included in the overview by the Sarcoma Meta-Analysis Collaboration (SMAC), which also included updated individual patient data.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Considering all resected soft tissue sarcoma patients, doxorubicin-based adjuvant chemotherapy significantly reduces all recurrences, with an absolute benefit of 10% (95% confidence interval, 5% to 15%; p=0.0001) at 10 years. There is only a non-significant effect for survival, with an absolute benefit of 4% at 10 years (95% confidence interval, 1% to 9%). Considering only patients with soft tissue sarcoma of the extremities, the benefit of adjuvant chemotherapy is 7% at 10 years (p=0.001).
- The final results of the small trials evaluating new regimens have since been fully published. One of the small randomized studies, which used a new regimen of high dose epirubicin and ifosfamide in large high-grade extremity sarcomas, showed improved disease free (p=0.04) and overall survival (p=0.03).

Subgroups Most Likely to Benefit:

Patients with soft tissue sarcoma of the extremities

POTENTIAL HARMS

Most chemotherapy regimens produce significant toxicity.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guideline did not consider non-anthracycline-based chemotherapy regimens or neoadjuvant chemotherapy.
- There is insufficient evidence on patients with retroperitoneal sarcomas or stromal tumours of the bowel to make recommendations for adjuvant chemotherapy. The risk of serious toxicity in retroperitoneal sarcomas when chemotherapy is combined with radiation therapy is of major concern. Similarly, the data on uterine sarcomas come from a single trial with negative results; therefore, no specific recommendations can be made about these tumours.
- Risks of severe persistent adverse effects of adjuvant chemotherapy, such as cardiomyopathy, should be carefully evaluated and balanced against the expected benefit, particularly in patients aged 70 years or older and those with significant co-morbidity.
- There are insufficient data to determine whether single-agent doxorubicin or combination chemotherapy with doxorubicin should be recommended. This decision should take into account issues such as patient preference/convenience, likely adverse effects, costs and available resources. Meta-analyses of trials evaluating adjuvant chemotherapy with single-agent doxorubicin and doxorubicin-based combination regimens, both compared with observation, showed similar results for mortality and recurrence. Many of the doxorubicin-based combination chemotherapy regimens examined in the trials are not considered very effective today. New regimens using high dose ifosfamide and epirubicin have reported significant advantages in preliminary trials. These results require confirmation in larger trials.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Figueredo A, Bramwell VHC, Bell R, Davis AM, Charette ML, Sarcoma Disease Site Group. Adjuvant chemotherapy following complete resection of soft tissue sarcoma in adults [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Oct. 27 p. (Practice guideline; no. 11-2). [43 references]

Figueredo A, Sarcoma Disease Site Group, Bramwell VH, Bell R, Davis AM, Charette ML. Adjuvant chemotherapy following complete resection of soft tissue sarcoma in adults: a clinical practice guideline. Sarcoma 2002;6:5-18. [41 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 (revised online 2002 Oct)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Sarcoma Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Sarcoma Disease Site Group (DSG) disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Adjuvant chemotherapy following complete resection of soft tissue sarcoma in adults. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2002 Oct. Various p. (Practice guideline; no. 11-2). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on March 20, 2003. The information was verified by the guideline developer on May 8, 2003.

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Date Modified: 11/8/2004


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